Applicant respectfully requests correction of the error on the Office Action Summary Sheet.

By the present communication claims 18 and 34 have been amended and new claims 36-38 have been added. Following entry of the present amendment, claims 3, 4, 18-21, 29, 31, 32, and 34-38 will be under examination.

Support for the amendments to claim 18 can be found in the specification including, for example, on page 23, line 25, through page 25, line 6; page 25, lines 28-30; page 38, line 15, through page 39, line 11; page 49, lines 15-35; and page 53, lines 18-21. Support for the amendments to claim 34 can be found in the specification including, for example, in claim 3 as originally filed; page 23, lines 25-30; page 33, lines 7-23; and page 58, line 12, through page, 59, line 9. Support for new claims 36 and 38 can be found in the specification including, for example, in claims 18 and 19 as filed; on page 6, lines 4-6; on page 28, lines 20-28; page 33, lines 4-8; page 46, lines 18-23; page 75, lines 24-27; and page 93, lines 17-19. Accordingly, the amendments and new claims do not introduce new matter. Therefore, entry of the amendments and new claims is respectfully requested. A marked-up version of the amended claims showing changes made is attached hereto as Appendix A.

Applicant wishes to bring to the Examiner's attention co-pending application 10/030,003, which is a U.S. national stage application, under 35 U.S.C. § 371, of international application PCT/US00/11372, filed April 27, 2000.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 34 stands rejected under 35 U.S.C. § 112, second paragraph, allegedly because it is unclear whether or not the claims recite a two step method of administering a nucleic acid to a lymphoid tissue *in vivo* and further targeting a cell *ex vivo*.

Applicant traverses the rejection and respectfully maintains that claim 34 is sufficiently clear in view of the teaching and guidance in the specification. Nevertheless, in order to further prosecution of this application, claim 34 has been amended to independent form. Applicant respectfully submits that claim 34 is sufficiently clear and definite. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Applicant respectfully traverses the rejection of claims 3-4, 18-21, 29, 31-32 and 34-35, under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Regarding B cell expression elements

Applicant respectfully disagrees with the position taken in the Office Action that the skilled artisan would require undue experimentation to predict the sequence of a B cell specific expression element other than the immunoglobulin heavy

chain promoter/enhancer. As acknowledged on page 3 of the Office Action, the Federal Circuit has held that "a specification need not disclose what is well known in the art" *Genentech Inc. v Novo Nordisk A/S*, 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (CAFC 1997) *quoting Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Applicant respectfully submits that B cell specific expression elements were known in the art as demonstrated, for example, by Maxwell et al., Cancer Res. 51:4299-4304 (1991). As acknowledged on page 9 of the Office Action, Maxwell et al. describes the immunoglobulin heavy chain promoter and enhancer and the κ-light chain promoter and enhancer at page 4299, page 4300 and Figure 1. Accordingly, in view of the teaching and guidance provided in the specification for using B cell specific expression elements (for example, on page 33, lines 8-22) and that which was known in the art regarding B cell specific expression elements, those skilled in the art would have been able to routinely use a variety of B cell specific expression elements.

Regarding nucleic acids useful in the methods

In regard to the alleged unpredictability in the art with respect to the use of any nucleic acid other than a plasmid or any promoter other than the heavy chain promoter, Applicant maintains that unpredictability is not an issue with respect to the claimed invention. The claims recite nucleic acids containing a B cell expression element and encoding one or more heterologous epitopes or polypeptides. The references by Verma et al., Eck et al., Deonarian et al. or Miller et al. are general

review articles which appear to describe some complications in selecting a promoter or vector. However, any unpredictability for selecting a vector or promoter as described in these general review articles is not applicable to the claimed invention because the claims explicitly recite a nucleic acid molecule comprising a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide or one or more heterologous epitopes. The method claims further recite that the heterologous polypeptide or the one or more heterologous epitopes are expressed in a B cell. Therefore, the claims are directed to vectors or promoters that express a polypeptide or one or more heterologous epitopes in a B cell, not to any unpredictable vectors or promoters described in Verma et al., Eck et al., Deonarian et al. or Miller et al.

Regarding routes of administration

Applicant respectfully disagrees with the position taken in the Office Action that administration of nucleic acids to a lymphoid tissue other than spleen would not generate an immune response as observed in spleen. Applicant maintains for the reasons of record and based on the teachings in the specification that those skilled in the art would have been able to stimulate an immune response by administering a nucleic acid to a lymphoid tissue, such as a lymph node. Further evidence corroborating the teaching and guidance provided in the specification is provided in the Declaration under 37 CFR § 1.132 by Dr. Zanetti, attached hereto as Exhibit A. In the Declaration, Dr. Zanetti asserts that lymphoid tissues share

properties in common that allow nucleic acids administered to lymphoid tissues to stimulate an immune response similar to that observed for administration to spleen. In view of the common properties of lymphoid tissues, those skilled in the art would have understood from the teaching and guidance provided in the specification that the methods exemplified for delivery of nucleic acids to spleen can also be performed with other lymphoid tissues.

In regard to claims 29 and 32 and the alleged unpredictability in the art with respect to targeted gene delivery and gene expression, Applicant maintains that unpredictability is not an issue with the claimed nucleic acid encoding one or more heterologous polypeptides that are expressed in a B cell. The references by Verma et al., Eck et al., Deonarian et al. or Miller et al. are general review articles which appear to describe some complications of *in vivo* gene targeting and expression. However, any unpredictability for *in vivo* targeting and expressing genes as described in these general review articles is not applicable to the claimed invention because the claims explicitly recite that the heterologous polypeptides is expressed in a B cell and are, therefore, directed to methods where the nucleic acids have been successfully targeted to a B cell and expressed by a B cell.

Further corroboration that the teaching and guidance provided in the specification would have enabled those skilled in the art to administer a nucleic acid by a variety of methods is provided in the Declaration under 37 C.F.R. § 1.132 by

Dr. Zanetti attached hereto as Exhibit B. The Declaration describes treatment of conditions using *in vivo* or *ex vivo* administration of nucleic acids. The results described in the Declaration demonstrate that intrasplenic administration of nucleic acids encoding an influenza A virus antigen or experimental allergic encephalomyelitis antigen stimulated immune responses that protected against lethal influenza A or experimental allergic encephalomyelitis, respectively. Intravenous administration of cells transfected ex vivo with nucleic acids encoding an influenza A virus antigen or Muc-1 tumor antigen stimulated immune responses that protected against lethal influenza A or tumor formation, respectively. Thus the results described in the Declaration corroborate the teachings in the specification that a variety of methods for delivering a nucleic acid to an individual can be used to treat a condition or stimulate an immune response.

Regarding treating conditions

In contrast to the assertion in the Office Action, the specification provides teaching and guidance for use of the claimed methods to treat a variety of conditions. Treatment of numerous conditions are exemplified including, but not limited to influenza A, malaria and Muc-1 tumor formation. In addition to examples describing treatment of influenza, malaria, and tumors bearing MUC-1 by intrasplenic administration of nucleic acids, the specification teaches treatment of a variety of conditions (see, for example, page 25, line 8, through page 26, line 22) and administration of DNA vaccines by a variety of routes (see, for

example, page 26, line 24, through page 27, line 16; and page 58, line 12, through page 59, line 9). In view of the teaching and guidance provided in the specification, those skilled in the art would have been able to treat a variety of conditions using the claimed methods.

Further corroboration that the teaching and guidance provided in the specification would have enabled those skilled in the art to treat a variety of conditions is provided by evidence in the form of a Declaration under 37 C.F.R. § 1.132 by Dr. Zanetti attached hereto as Exhibit B. The Declaration describes use of the claimed methods to induce protective immunity against influenza A virus infection, corroborating the teaching in the specification that the invention can be used to stimulate an immune response against infectious agents (see, for example, page 25, lines 8-26). The Declaration also describes use of the claimed methods to induce protective immunity against experimental allergic encephalomyelitis, corroborating the teaching in the specification that the invention can be used to stimulate a protective immune response against an autoimmune disease (see, for example, page 25, line 27, through page 26, line 22). Furthermore, the Declaration describes use of the claimed methods to induce protective immunity against B16-MUC.1 tumors, corroborating the teaching in the specification that the invention can be used to stimulate an immune response against a tumor (see, for example, page 25, line 27, through page 26, line 22). Thus, the results described in the Declaration corroborate the teaching in the specification that the claimed methods can be

used to treat a variety of conditions as taught in the specification.

In view of the teaching and guidance provided in the specification and the evidence provided in Exhibits A and B, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Applicant respectfully traverses the rejection of claims 18 and 19 under 35 U.S.C. § 102(b), as allegedly anticipated by Maxwell et al., Cancer Res. 51:4299-4304 (1991). Claims 18 and 19, as amended, recite an antigen that functions as a vaccine. In contrast, Maxwell et al. describes expression plasmids containing the diptheria toxin A gene linked with promoters and enhancers from immunoglobulin heavy chain or κ-light chain genes. Because diptheria toxin A expressed from plasmids is toxic to B-cells as well as other cells (see for example, the first paragraph on page 4299 of Maxwell et al.), the toxin can not function as a vaccine. Therefore, Maxwell et al. does not anticipate claims 18 and 19. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 3-4, 29-31 and 35 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious over Hurpin et al., Vaccine

16:208-215 (1998) in view of Banerji et al., Cell 33:729-740 (1983) The Office Action alleges that Banerji et al. provides motivation to substitute a B-cell specific enhancer for the viral elements used by Hurpin et al. because Banerji et al. describes a two fold increase in expression for β globin under the control of a B-cell specific enhancer compared to the SV40 enhancer and increased expression would be desired in order to increase an immune response in the methods of Hurpin et al. The Office Action further alleges that the large percentage of B cells in the spleen provide further motivation for utilizing a B cell specific expression element in the method of Hurpin et al.

Applicant respectfully traverses the rejection. Applicant maintains, as set forth on the record, that the combination of cited references would not have provided motivation to modify the plasmid or vector of Hurpin et al. because Hurpin et al. describes induction of CTLs at satisfactory levels with the CMV promoter and Banerji et al. merely describes expression of a β globin gene but does not teach or suggest inducing CTLs to any gene, much less increasing CTLs over satisfactory levels. Absent a teaching or suggestion in the combination of references to increase CTL levels over the satisfactory levels obtained by Hurpin et al., there is no motivation to modify the vector or plasmid of Hurpin et al.

Furthermore, those skilled in the art would not have been motivated to modify the vector of Hurpin et al. to include a B cell expression element because the references do not provide a

reasonable expectation of success that such a vector, when administered in the methods of Hurpin et al., would raise an immune response. There is no teaching or suggestion in the combination of references that B cells are capable of taking up nucleic acids in the methods of Hurpin et al. because Hurpin et al. merely describes intrasplenic administration of nucleic acids without identifying what types of cells take up the nucleic acids and Banerji et al. is not directed to intrasplenic administration of any nucleic acids. Although Banerji et al. describes chloroquine diphosphate induced transfection of B lymphocytes in culture, the reference even when taken in combination with Hurpin et al. does not teach or suggest that transfection of B lymphocytes using chloroquine diphosphate *in vitro* is indicative of spontaneous uptake of nucleic acids by B cells under conditions of intrasplenic administration.

Moreover, the mere knowledge that B cells were abundant in the spleen would not have suggested that B cells were the targeted population in the methods of Hurpin et al. or that other cells did not take up nucleic acids in the methods of Hurpin et al. Absent a teaching or suggestion that the nucleic acid of Hurpin et al. targeted B cells over other spleen cells, those skilled in the art would not have had motivation to combine Hurpin et al. with Banerji et al. nor would they have had a reasonable expectation of success that using a B-cell specific expression element, thereby excluding other spleen cells from producing antigen, would induce an immune response. Furthermore, those skilled in the art would not have had a reasonable expectation that using a B-cell specific expression element to

exclude other spleen cells from producing antigen would increase the immune response over that obtained with a viral promoter expected to express in a variety of spleen cells. Thus, there would have been no motivation to modify the vector of Hurpin et al.

For the reasons set forth above, the claimed methods would not have been obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned agent or Cathryn Campbell if there are any questions.

Respectfully submitted,

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Appendix A

A marked up version showing changes made to the claims follows. Text to be added is underlined and text to be deleted is in brackets.

18. (Amended) A nucleic acid molecule comprising a B cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide antigen, wherein said B cell expression element comprises a B cell promoter and enhancer, wherein said antigen functions as a vaccine.

34. (Amended) A method for stimulating an immune response [The method of claim 3], comprising [wherein said] targeting a nucleic acid molecule to a B cell *ex vivo* and administering said B cell [is administered] to an individual [said lymphoid tissue and targeted to a cell *ex vivo*, and said targeted cell is then administered to an individual], wherein said nucleic acid molecule comprises a B cell expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, and wherein said one or more heterologous epitopes are expressed in said B cell.